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HORLICK,K

EXAMINER

18M2/0702

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Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

SEE ATTACHED OFFICE ACTION

Office Action Summary	Application No. 08/235,411	Applicant(s) Woudenberg et al.
	Examiner Kenneth R. Horlick	Group Art Unit 1807

☒ Responsive to communication(s) filed on *Mar 1, 1996* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *13-38* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *13-38* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claims 17 and 24-38 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 17 is confusing because it depends from claim 15, and "the removable reaction chamber" does not have proper antecedent basis.

B) Claim 25 is confusing because it is grammatically incorrect; that is, it does not recite a complete sentence.

C) Claims 24-38 are confusing because of the language in claims 24, 36 and 38, "proportional to the concentration of amplification reaction product in the sample and the volume of the sample". Contrary to this language, the specification describes methods in which the first fluorescent signal has an intensity which is proportional to the concentration of amplification product (not the volume), and the second fluorescent signal has an intensity which is proportional to the volume. Clarification is required.

D) Claims 24-38 are further confusing because the methods are for "monitoring the formation of a nucleic acid amplification reaction product in real time", but the independent claims do not actively recite any step wherein such a product is formed. That is, the claims merely require a step of adding a sample which contains a nucleic acid to be amplified; this is clearly not an amplification step. Put another way, the claims have no basis for "amplification reaction product in the sample"

E) Claim 28 is further confusing because "the lens" does not have proper antecedent basis.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 13-14 are rejected under 35 U.S.C. § 102(a) as being anticipated by either Burg et al. or Higuchi et al. (1993).

These claims are drawn to an apparatus comprising: a sample holder; a fiber optic cable; a lens co-axially disposed with the fiber optic cable; and a detection and analysis mechanism (the remainder of the language recited in claim 13, i.e. first and second fluorescent signals, is directed towards an "intended use" of the apparatus and need not be addressed in the rejection).

Both Burg et al. (see abstract and fig. 1) and Higuchi et al. (1993)(see entire reference, especially the abstract and fig. 1 on page 1026) teach an apparatus comprising: a sample holder; a fiber optic cable; a lens co-axially disposed with the fiber optic cable; and a detection and analysis mechanism.

3. Claims 24-25, 27, 33, and 35 are rejected under 35 U.S.C. § 102(a) as being anticipated by Lee et al.

These claims are drawn to methods comprising: adding a sample to a sample holder containing a nucleic acid to be amplified; exciting the sample via a beam, wherein said sample comprises a first fluorescent indicator for which fluorescence intensity is proportional to the concentration of amplification product in the sample, and a second fluorescent indicator for which fluorescence intensity is proportional to the volume of the sample; and measuring the intensities of the first and second fluorescent signals. Claim 35 is drawn to such a method, wherein the first and second fluorescent indicators are covalently attached to an oligonucleotide having a sequence complementary to a portion of a strand of the amplification product, the second fluorescent indicator quenching the fluorescence of the first indicator.

Lee et al. teach a method comprising: adding a sample to a sample holder containing a nucleic acid to be amplified; exciting the sample via a beam, wherein said sample comprises a first fluorescent indicator for which fluorescence intensity is proportional to the concentration of amplification product in the sample, and a second fluorescent indicator for which fluorescence intensity is proportional to the volume of the sample; and measuring the intensities of the first and second fluorescent signals (see entire reference, especially fig. 1 and "Results" on pages 3762-3763). Lee et al. further teach said method regarding PCR, wherein the first and second fluorescent indicators are covalently attached to an oligonucleotide having a sequence complementary to a portion of a strand of the amplification product, the second fluorescent indicator quenching the fluorescence of the first indicator. This reference specifically teaches at the top right-hand side of page 3763 that "TMR

fluorescence can be used as an internal fluorescence reference to control for pipetting errors and evaporation during thermal cycling". It is taught in the last paragraph on page 3766 that fluorescence be detected directly in a closed reaction vessel.

4. Claims 13-14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Higuchi et al. (1992).

These claims are drawn to an apparatus comprising: a sample holder; a fiber optic cable; a lens co-axially disposed with the fiber optic cable; and a detection and analysis mechanism (the remainder of the language recited in claim 13, i.e. first and second fluorescent signals, is directed towards an "intended use" of the apparatus and need not be addressed in the rejection).

Higuchi et al. (1992) teach an apparatus comprising: a sample holder; a fiber optic cable; a lens co-axially disposed with the fiber optic cable; and a detection and analysis mechanism (see entire reference, especially first full paragraph and fig. 5 on page 415).

5. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same

person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 13-34 and 36 are rejected under 35 U.S.C. § 103 as being unpatentable over either Burg et al. or Higuchi et al. (1993), in view of either Gershoni et al. or Krause et al.

Claims 13-23 are drawn to an apparatus comprising: a sample holder; a fiber optic cable; a lens co-axially disposed with the fiber optic cable; and a detection and analysis mechanism (the remainder of the language recited in claim 13, i.e. first and second fluorescent signals, is directed towards an "intended use" of the apparatus and need not be addressed). Claims 24-34 are drawn to methods of using said apparatus comprising: adding a sample to the sample holder containing a nucleic acid to be amplified; exciting the sample via a beam, wherein said sample comprises a first fluorescent indicator for which fluorescence intensity is proportional to the concentration of amplification product in the sample, and a second fluorescent indicator for which fluorescence intensity is proportional to the volume of the sample; and measuring the intensities of the first and second fluorescent signals. Claim 36 is drawn to such a method, wherein a plurality of sample holders are used.

Both Burg et al. (see abstract and fig. 1) and Higuchi et al. (1993)(see entire reference, especially the abstract and fig. 1 on page 1026) teach an apparatus comprising: a sample holder; a fiber optic cable; a lens co-axially disposed with the fiber

optic cable; and a detection and analysis mechanism. These references also teach using such an apparatus for the real time fluorescence detection of products in amplification reactions. Higuchi et al. also teach normalization of fluorescence for quantitative analysis, to compensate for measurement variation, on page 1027, last paragraph, to page 1028, last full paragraph in first column. This reference suggests the use of other means of minimizing sample-to-sample fluorescence variation in the final paragraph on page 1030.

Neither of these references teach the use of a second fluorescent indicator capable of generating a signal proportional to the volume of the reaction mixture, to be used as an internal standard. Nor do the references teach an apparatus with all of the limitations of the dependent claims.

Gershoni et al. teach measuring fluorescence of a target molecule in the presence of a second fluorescent molecule, which is used as an internal standard to account for measurement variation (see abstract and introduction on pages 315-316). Krause et al. provide the same teaching, including the use of one of the preferred dyes, fluorescein (see entire reference, especially "Materials and Methods" on page 170).

One of ordinary skill in the art would have been motivated to use a second fluorescent dye as an internal standard in the method of Burg et al. or Higuchi et al. (1993) because this would have been expected to provide more accurate quantitative measurements, as suggested by Gershoni et al. or Krause et al. Further, the skilled artisan would have been motivated to modify the apparatus of these methods in the claimed manner because such modifications are slight and would have been expected to provide a functionally equivalent apparatus, or one with predictable and expected improvements. For example, removable, sealable cuvettes were commonly used in the art, and would have been an obvious choice for use in amplification reactions, for which

contamination was a well known problem. Further, as it was well known that amplification reactions involve elevated temperatures or temperature cycles including elevated temperatures, a heating element to warm the optical interface would have been an obvious way to avoid the expected problem of condensation, which would interfere with light transmission. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make and use the claimed apparatus, and to carry out the claimed methods.

6. Claims 13-34 and 36 are rejected under 35 U.S.C. § 103 as being unpatentable over Higuchi et al. (1992), in view of either Gershoni et al. or Krause et al.

These claims are drawn to an apparatus and method of use thereof as described *supra*.

Higuchi et al. (1992) teach an apparatus comprising: a sample holder; a fiber optic cable; a lens co-axially disposed with the fiber optic cable; and a detection and analysis mechanism (see entire reference, especially first full paragraph and fig. 5 on page 415). This references also teaches using such an apparatus for the real time fluorescence detection of products in amplification reactions.

This reference does not teach the use of a second fluorescent indicator capable of generating a signal proportional to the volume of the reaction mixture, to be used as an internal standard. Nor does it teach an apparatus with all of the limitations of the dependent claims.

Gershoni et al. teach measuring fluorescence of a target molecule in the presence of a second fluorescent molecule, which is used as an internal standard to account for measurement variation (see abstract and introduction on pages 315-316).

Krause et al. provide the same teaching, including the use of one of the preferred dyes, fluorescein (see entire reference, especially "Materials and Methods" on page 170).

One of ordinary skill in the art would have been motivated to use a second fluorescent dye as an internal standard in the method of Higuchi et al. (1992) because this would have been expected to provide more accurate quantitative measurements, as suggested by Gershoni et al. or Krause et al. Further, the skilled artisan would have been motivated to modify the apparatus of the reference in the claimed manner because such modifications are slight and would have been expected to provide a functionally equivalent apparatus, or one with predictable and expected improvements. For example, removable, sealable cuvettes were commonly used in the art, and would have been an obvious choice for use in amplification reactions, for which contamination was a well known problem. Further, as it was well known that amplification reactions involve elevated temperatures or temperature cycles including elevated temperatures, a heating element to warm the optical interface would have been an obvious way to avoid the expected problem of condensation, which would interfere with light transmission. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make and use the claimed apparatus, and to carry out the claimed methods.

7. Claims 37-38 are rejected under 35 U.S.C. § 103 as being unpatentable over any one of Burg et al., Higuchi et al. (1993), or Higuchi et al. (1992), in view of either Gershoni et al. or Krause et al., and further in view of Renzoni et al.

These claims are drawn to the methods described *supra*, with the added limitation of using a plurality of first fluorescent indicators each corresponding to a different amplification product.

The teachings of the primary and secondary references are discussed *supra*.

These references do not teach the use of a plurality of first fluorescent indicators.

Renzoni et al. disclose the simultaneous detection of two or more different nucleic acids by labeling each such nucleic acid with a distinguishable fluorescent label (see column 16, line 66 to column 17, line 36).

One of ordinary skill in the art would have been motivated to use a second fluorescent dye as an internal standard in the method of any one of the primary references because this would have been expected to provide more accurate quantitative measurements, as suggested by Gershoni et al. or Krause et al. The artisan of ordinary skill would have been further motivated to use a plurality of first fluorescent indicators because this would have been expected to facilitate simultaneous detection of multiple nucleic acids, thus providing more information than only use of a single indicator (Renzoni et al.). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to carry out the claimed methods.

8. Claims 26, 28-32, 34, and 36 are rejected under 35 U.S.C. § 103 as being unpatentable over Lee et al. in view of any one of Burg et al., Higuchi et al. (1993), or Higuchi et al. (1992).

These claims are drawn to the methods as described *supra*, with further limitations regarding the means by which fluorescence is detected.

The teachings of Lee et al. are discussed *supra*.

Lee et al. do not teach the use of complex forming dyes, an optical interface with heating means, nor ligase chain reaction.

Burg et al., Higuchi et al. (1993), and Higuchi et al.

(1992) each teach the use of a complex forming dye and a fiber optic interface to detect fluorescence in polymerase chain reaction amplification assays (see *supra*).

One of ordinary skill in the art would have been motivated to use a complex forming dye, and an optical interface as a detection means, in the method of Lee et al. because each of the secondary references teaches the use of fiber optics for detecting fluorescence in amplification assays. Further, the ligase chain reaction was well known and common knowledge in the art, and would have clearly been an obvious application for such methods. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to carry out the claimed methods.

9. Claims 37-38 are rejected under 35 U.S.C. § 103 as being unpatentable over Lee et al. in view of Renzoni et al.

These claims are drawn to methods as described *supra*, with the added limitation of a plurality of first fluorescent indicators each corresponding to a different amplification product.

The teachings of Lee et al. are discussed *supra*.

This reference does not teach the use of a plurality of first fluorescent indicators.

Renzoni et al. disclose the simultaneous detection of two or more different nucleic acids by labeling each such nucleic acid with a distinguishable fluorescent label (see column 16, line 66 to column 17, line 36).

One of ordinary skill in the art would have been motivated to use a plurality of first fluorescent indicators in the method of Lee et al. because this would have been expected to facilitate simultaneous detection of multiple nucleic acids, thus providing more information than only use of a single indicator (Renzoni et al.). It would have been prima facie obvious to one of ordinary

skill in the art at the time the invention was made to carry out the claimed methods.

10. The arguments of the response filed 01 March 1996, as they apply to the new claims, have been fully considered but are not found persuasive

The response argues that neither Krause et al. nor Gershoni et al. should be considered prior art because they are non-analogous art, and are not pertinent to the particular problem with which the invention is involved. This is not found convincing because both of these references do address the problem of the instant invention: correcting for errors in measurements of fluorescence. While the particular reactions and conditions are different, it is nevertheless clear that the problem of variations in fluorescence measurements was known in the art, as was the solution of adding an internal standard (the exact manner in which an internal standard is best used in any particular reaction would have been well within the grasp of one of ordinary skill in the art).

A Katz-type declaration was submitted with said response for the purpose of eliminating Lee et al. as prior art under 35 U.S.C. 102(a). However, the declaration is not effective for this purpose. Even if author Bloch was not involved in the work in Lee et al. pertaining to the instant invention, Lee and Connell are still "others" with respect to the instant inventive entity of Woudenberg, Bodner, Connell, Ganz, McBride, Saviano, Shigeura, Tracy, Young, and Lee.

11. No claims are allowable over the prior art.

12. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Kenneth Horlick whose telephone number is (703) 308-3905. The examiner can normally be reached on Monday-Thursday from 6:30 AM-4:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for Art Unit 1807 is (703) 305-7401.

KENNETH R. HORLICK
PATENT EXAMINER
GROUP 1800

Kenneth R. Horlick, Ph.D.
6/27/96